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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/660,811 09/12/2003 Laurence Rahme 00786/435003 7444

21559 7590 12/29/2006
CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER

DUFFY, PATRICIA ANN

ART UNIT	PAPER NUMBER
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1645

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS 12/29/2006 PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/660,811	RAHME ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 1-14 and 23-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input checked="" type="checkbox"/> Other: <u>sequence alignments 4 pages</u> . |

DETAILED ACTION

The response filed 10-4-06 has been entered into the record.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application, by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration for inventor Jens Slosbacher. See 37 CFR 1.52(c).

Information Disclosure Statement

The information disclosure statement filed 4-4-05 has been considered. A initialed copy is enclosed.

Election/Restrictions

Applicant's election with traverse of the polypeptide of SEQ ID NO:141 (claims 15-22 in the response filed 10-2-06 is acknowledged. The traversal is on the ground(s) that the MPEP allows for search and examination of up to ten (10) independent sequences and the search and examination of 4-7 would not be unduly burdensome. This is not found

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persuasive because the Office has provided for such at MPEP 803.04. This is not persuasive, the claims are first not drawn to nucleic acids and second, since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature essential to that utility. In the instant case the polypeptides fail to share a "substantial structure feature" in common, as essential to the disclosed utility. The search and examination of multiple independent inventions that a common core structure or substantial structural feature in common as essential to the disclosed utility would, in fact be a burden on the examiner and the office. The requirement is still deemed proper and is therefore made FINAL.

Claims 1-14, 15-22 (in part) and 23-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and polypeptide species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 10-4-06

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 16 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification broadly describes as part of the invention "pathogenic virulence factors" such as RL038 (SEQ ID NO:141, pages 2-3 of the specification). The specification also broadly describes their novel proteins by a novel reference polynucleotide sequence of SEQ ID NO:17. Applicants also broadly describe the invention as embracing any substitution, insertion or deletion change of nucleotides or amino acids throughout the entire stretch of nucleotides found in the encoding or reference sequence by use of language in which a specified percent of amino acids can be changed in the polypeptide. None of these sequences meets the written description provision of 35 USC 112, first paragraph. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.).

The specification only discloses a polynucleotide sequence consisting of SEQ ID NO: 17 which corresponds to the polynucleic acid sequence encoding the *Pseudomonas aeruginosa PA14* species of the protein "RL038" which is an alleged pathogenic virulence

factor comprising the amino acid sequence set forth in SEQ ID NO:141. Applicants have not described nor disclosed any variants of the protein or the encoding nucleic acid. The specification fails to teach a single variant of a polypeptide sequence of SEQ ID NO:141 and it is noted that the claimed protein does as an invention independent of their function as an antigen for generating an antibody useful for diagnosis or detection of the pathogenic virulence factor and the microorganism per se. The actual structure or other relevant identifying characteristics of each variant protein having the claimed properties of an RL038 protein can only be determined empirically by actually making every nucleic acid that encodes the recited variability (i.e. the instant 70% identity) and testing each to determine whether it encodes a protein having the particularly disclosed properties of an RL038 protein. As noted in the Guidelines at Section I.A.(2):

There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

Applicants' specification proposes the converse, yet still does not meet the requirements for an adequate written description of the claimed invention. The RL038 protein is a putative virulence factor and has specific biological properties dictated by the structure of the protein and the corresponding structure of the structural gene sequence that encodes it. There must be some nexus between the structure of a gene sequence, the structure of the protein encoded, and the function of that encoded protein. However, function cannot be predicted from the modification of the structure of the gene or in this case the gene encoding the protein. Applicants have not shown that, by modifying a reference sequence encoding a reference polypeptide as claimed, will automatically predict the production of a RL038 protein as disclosed. While it is true that, due to the nature of codon degeneracy, applicant may take a reference sequence and modify that sequence to

be a different nucleic acid sequence, yet still have that nucleic acid encode the same RL038 protein. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of a representative number of RL038 proteins, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. In the instant case, the specification provides only written description for a protein comprising the amino acid sequence as set forth in SEQ ID NO:141 (RL038), the skilled artisan cannot envision all the contemplated sequences by the detailed chemical structure of the claimed polynucleotides and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Claims 15-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substantially pure protein comprising the amino acid sequence set forth in SEQ ID NO:141, the specification does not reasonably provide enablement for percent identical variants, human protein binding variants or variants with a Arg-Gly-Asp motif. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to and encompass proteins which comprise a sequence which has a recited percent identity or average variability as compared to a sequence comprising SEQ ID NO:141 (RL038). These claims are not enabled for the following reasons. The

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written description is limited to only SEQ ID NO:141 which is the corresponding amino acid sequence encoded by the polynucleotide comprising SEQ ID NO:17. The specification fails to indicate that SEQ ID NO:141 has any virulence as measured by any known or established assay for biological activity and further lacks any description of any variants for fragments which function as diagnostics, bind human lung proteins or comprise the Arg-Gly-Asp motif. The specification is not enabled for any variants of the amino acid sequence of the protein of SEQ ID NO:141, because 1) the specification fails to teach that the alleged RL038 has the ability to function as virulence factor in any biological assay. 2) the specification lacks any written description of any specific assay conditions, such as substrate, pH, temperature etc., which could be used to determine working embodiments within the scope of percent identical variants of the RL038 protein comprising the amino acid sequence set forth in SEQ ID NO:141 which are encompassed by the language of the claims; 3) the specification fails to teach how to make and use n proteins variants or fragments thereof that have an unknown, non-assayable function; 4) the specification fails to teach what are the critical protein residues that can be modified and still achieve a protein with similar functional ((i.e., virulence or diagnostic characteristics for the *Pseudomonas aeruginosa*; 5) the art teaches that polynucleotides isolated based on percent homology do not predictably display the functions of their homologs and in the absence of a demonstration that SEQ ID NO:141 has the ability to act as a virulence protein; 6) the art teaches that proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, one skilled in the art would have reason to doubt the validity and functionality of the function of the protein variants of SEQ ID NO:141 and diagnostic use of variants thereof and 7) applicants have not displayed a nexus between the structure of the gene sequence and function of the protein as either a virulence factor or as a diagnostic protein.

As to points 1)- 7), the specification fails to provide a written description of any protein fragments (i.e. the mature form, prepro form, the pro form) or protein variants by percent identity to the bacterial protein sequence of SEQ ID NO:141, which function equivalently to a polypeptide comprising the disclosed SEQ ID NO:141 or are able to be used as a diagnostic. The specification fails to teach the critical protein residues involved in the function of the protein SEQ ID NO:141, such that the skilled artisan is provided no guidance to test, screen or make nucleic acid sequence variants of the polynucleic acids encoding the variants of the polypeptide of comprising SEQ ID NO:141 or the polynucleotide comprising SEQ ID NO:17, using conventional technology which allow for a screening or generic diagnostic use asserted in the specification. The specification fails to teach to what extent you could alter SEQ ID NO:141 and still present the sequence as diagnostic. In order to be diagnostic the sequence must distinguish *Pseudomonas aeruginosa* from non-pathogenic sp. and other clinically relevant autochthonous bacteria in a host. One skilled in the art would have reason to doubt the alleged function of the protein and polynucleic acid encoding the protein because the specification fails to teach that the protein produced by the DNA actually functions as asserted and the art teaches that polynucleotides isolated based on percent homology do not predictably display the functions of their homologs (Herzog et al, DNA and Cell Biology, 12(6):465-471, 1993; see abstract and Jazin et al., Regulatory Peptides, 47:247-258, 1993, see summary). Attwood et al teaches that "...it is presumptuous to make functional assignments merely based on the basis of some degree of similarity between sequences (and it is not always clear what we mean by "function")..." (Science, 290:471-473, 2000 at pager 471, column 1, second full paragraph). Even if one were to demonstrate that SEQ ID NO:141 functioned as a virulence factor, the specification is not enabled for polynucleotides encoding protein variants because the specification fails to teach even one substrate and assay which one skilled in the art could use to screen for protein variants of SEQ ID NO:141. No assay for function or guidance for setting forth parameters of a functional assay is set forth in the

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specification which would allow one skilled in the art to screen for functionally equivalent variants of either the protein or diagnostic use and the specification does not specifically point to a particular one in the art would could be relied upon for screening for polypeptides and polynucleotides encoding them for diagnostic or screening use. One of skill in the art would be reduced to merely randomly altering nucleic acids and amino acid(s) which would lead to unpredictable results regarding the functional activity of the protein and the ability of the nucleic acid to be used as a diagnostic and one skilled in the art would be unable to test for functionality of the polynucleotide encoding the variants of the polynucleotide of SEQ ID NO:17 and polynucleotides encoding the variants of the protein encoded by SEQ ID NO:141. Thus, one skilled in the art could not even screen for working embodiments within the scope of the claim because no assay is set forth in the specification. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted *a priori* and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3):1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of

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a single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol., 1991, 5(7):1755-67) teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Applicants have not taught which residues of SEQ ID NO:141 can be varied and still achieve a protein that is functional as an virulence factor or is capable of use as a diagnostic using immunological means of recognition. Further, while the specification teaches use of the proteins to make antibodies for diagnostics, the art is replete with teachings that variation of a sequence of a protein can ablate antibody binding and specificity of any antibody as a diagnostic agent as exemplified by Jobling et al. The specification has not conceived any other functionally equivalent protein variant that is a virulence factor, that binds a human protein or human lung protein or has an Arg-Gly-Asp motif, does not set forth the general tolerance to substitutions, where substitutions could be made and how particularly to assay for these variants. Since, the specification lacks a written description of any variant comprising SEQ ID NO:141, it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed protein variants of SEQ ID NO:141 respectively, as well as the screening method of obtaining them, as well as how to use the polynucleotides encoding the protein variants, one of skill in the art would be unable to produce these polynucleotides encoding protein variants or polynucleotide variants encompassed by the instant claims. Herzog et al, and Jazin et al of record teach that polynucleotides isolated based on percent homology do not predictably display the functions of their homologs absent some independent teaching that the sequence produces a protein that functions as alleged. Thus, biological function ascribed the gene product based on solely structural or sequence identity is unreliable and unpredictable in the absence of supporting production

of the protein and functional analysis. Thus there is no evidentiary support that the instant protein functions as an diagnostic or virulence factor. The protein has specific immunological and biological properties which are the result of its primary acid sequence as encoded by this nucleic acid sequence. Applicants' proposed insertions, deletions or substitutions to that nucleic acid sequence do not predict a protein having all the identifiable properties of the RL038 protein as disclosed. Therefore, such undisclosed and unidentified nucleic acids which result from these, insertions, deletions or substitutions encompasses by the recited "at least 25 or 50 or 70% identical etc " are not enabled for their scope. The skilled artisan would be forced into undue experimentation to make and use the instantly claimed scope of invention. Although the skilled artisan might envision making a great number of changes of a reference nucleic acid sequence in accordance with applicant's disclosure, it is unclear exactly that the protein which is expresses therefrom would be the RL038 protein disclosed as applicants' invention. These altered proteins would vary from the disclosed RL038 amino acid sequence of SEQ ID NO:141 in some unknown or unpredictable manner. *Amgen Inc. v. Chugai Pharmaceutical Co. Inc.* 18 USPQ2d 1016, 1026 (CAFC 1991) addressed a similar issue of enablement and undue experimentation for analogs of erythropoietin (EPO) gene broadly claimed and narrowly disclosed. See also *In re Duel* 34 USPQ2d 1210 (CAFC 1995); *Colbert v. Lofdahl* 21 USPQ2d 1068 (Bd. Pat. Ap. Inter. 1991); and *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997).

In view of the lack of written description of any protein variant that functions equivalently to the protein of SEQ ID NO:141, the lack of enabling description of make and use protein variants of SEQ ID NO:141, the lack of teaching even a beginning point for variation of the nucleic acid corresponding to a variant of the protein sequence of SEQ ID NO:141 for routine experimentation, the lack of an assay to screen for variants, lack of working examples commensurate in scope with the instant claims, the skilled artisan

would be forced into undue experimentation to practice (i.e. make and use) the invention as is broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or

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indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 15-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Ausubel et al) WO 03/0048689, published January 16, 2003 with priority to 60/373,233 filed April 16, 2002 for SEQ ID NO:6) or by Ausubel et al (US2005020424A1 with priority to April 14, 1002 for SEQ ID NO:6).

It is noted that the recitation of "an amino acid sequence" has been interpreted as reading on any subsequence thereof.

Ausubel et al teach a polypeptide of SEQ ID NO:6. The polypeptide of SEQ ID NO:6 is a virulence protein from *Pseudomonas* is 48.4% identical as compared to the full-length of SEQ ID NO:141. Ausubel et al teach that amino acid residues 1-526 of the polypeptide as set forth in SEQ ID NO:6 is 99% identical to residues 64-589 of the polypeptide as set forth in SEQ ID NO:141. The function of binding is inherent to the structure.

Status of the Claims

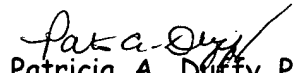
Claims 15-22 stand rejected. Claims 1-14 and 23-26 are withdrawn from consideration.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Examiner Jeffrey Siew can be reached on 571-272-0787.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.


Patricia A. Duffy, Ph.D.

Primary Examiner

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SEQUENCE

Page 1

Db 1021 PKGLQQDLHRMAGSLAVMRARTLVVMCQGAEEGLLESRLCSAVEIGEVLVHIEQALEFV 1080
 QY 1081 RKTG 1084
 Db 1081 RKTG 1084

ALIGNMENT

RESULT 2

US-10-482-948-6

; Sequence 6, Application US/10482948

; Publication No. US20050202424A1

GENERAL INFORMATION:

; APPLICANT: AUSUBEL, FREDERICK M.

; APPLICANT: DRENKARD, ELIANA

; TITLE OF INVENTION: Regulators of Biofilm Formation and Uses

; TITLE OF INVENTION: Thereof

; FILE REFERENCE: 00786/398004

; CURRENT APPLICATION NUMBER: US/10/482,948

; CURRENT FILING DATE: 2004-01-06

; PRIOR APPLICATION NUMBER: PCT/US02/21431

; PRIOR FILING DATE: 2002-07-08

; PRIOR APPLICATION NUMBER: US 60/373,233

; PRIOR FILING DATE: 2002-04-16

; PRIOR APPLICATION NUMBER: US 60/303,286

; PRIOR FILING DATE: 2001-07-06

; NUMBER OF SEQ ID NOS: 39

; SOFTWARE: FastSEQ for Windows Version 4.0

; SEQ ID NO 6

; LENGTH: 664

; TYPE: PRT

; ORGANISM: Pseudomonas aeruginosa PA14

US-10-482-948-6

Query Match 48.4%; Score 2685; DB 5; Length 664;

Best Local Similarity 81.5%; Pred. No. 4.9e-218;

Matches 550; Conservative 17; Mismatches 58; Indels 50; Gaps 5;

QY 64 MMDVIREHEVFLGRIARSDKTTQKYDYDVVPLQRHLLAKENGLAVYEGREFSFAMPFLL 123
 Db 1 MMDVIREHEVFLGRIARSDKTTQKYDYDVVPLQRHLLAKENGLAVYEGREFSFAMPFLL 60
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 Db 61 ATKHALSADSSGDPFSLGVLLANFYGSFWSVSAYPAPQLLIFDLSGSTR LAVPSIPSTAQ 120
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 Db 361 NWKLF DARGQVPGDICIQVGGRYLQTAF AATRYAGTEAVLCVFNDITVHCEAETALSNAK 420
 QY 484 RAADAASQAKTLFLARMSHEIRTPLYGVLGTLELLDLTTLNERQRAYLRITQSSSATLMQ 543


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Db      574 Lfq-----LQRRLV AHLHEDDRQAPRSGVRRRLGSDPGQVHHIGIVLH-- 616
Qy      718 EDEQSGLACRPGLLK 732
Db      617 RDSPATLAAAHGMAK 631

```

RESULT 3

US-10-482-948-35

; Sequence 35, Application US/10482948

; Publication No. US20050202424A1

GENERAL INFORMATION:

; APPLICANT: AUSUBEL, FREDERICK M.

; APPLICANT: DRENKARD, ELIANA

; TITLE OF INVENTION: Regulators of Biofilm Formation and Uses

; TITLE OF INVENTION: Thereof

; FILE REFERENCE: 00786/398004

; CURRENT APPLICATION NUMBER: US/10/482,948

; CURRENT FILING DATE: 2004-01-06

; PRIOR APPLICATION NUMBER: PCT/US02/21431

; PRIOR FILING DATE: 2002-07-08

; PRIOR APPLICATION NUMBER: US 60/373,233

; PRIOR FILING DATE: 2002-04-16

; PRIOR APPLICATION NUMBER: US 60/303,286

; PRIOR FILING DATE: 2001-07-06

; NUMBER OF SEQ ID NOS: 39

; SOFTWARE: FastSEQ for Windows Version 4.0

; SEQ ID NO 35

; LENGTH: 663

; TYPE: PRT

; ORGANISM: Pseudomonas aeruginosa PA14

US-10-482-948-35

Query Match 48.3%; Score 2680; DB 5; Length 663;

Best Local Similarity 81.5%; Pred. No. 1.3e-217;

Matches 549; Conservative 17; Mismatches 58; Indels 50; Gaps 5;

```

Qy      65 MDVIREHEVFLGRIARKSDKTTQKYDYDVVPLQRHLLAKENGLAVYEGREFSFAMPFLLA 124
Db      1 MDVIREHEVFLGRIARKSDKTTQKYDYDVVPLQRHLLAKENGLAVYEGREFSFAMPFLLA 60
Qy      125 TKHALSADSSGDPFSLGVLLANFYGSFWSVSAYPAPQLLIFDLSGSTR LAVPSIPSTAQR 184
Db      61 TKHALSADSSGDPFSLGVLLANFYGSFWSVSAYPAPQLLIFDLSGSTR LAVPSIPSTAQR 120
Qy      185 DRLSGSYPMIVERILARLRTRPVGEDAQRVHWIRADRYRDSALEMLGVARVDLPETLWWH 244
Db      121 DRLSGSYPMIVERILARLRTRPVGEDAQRVHWIRADRYRDSALEMLGVARVDLPETLWWH 180
Qy      245 DEPNHLIIAASLLDLRRINDFEQLVERPAFDSYSLVSPDGEVLLGAAPATGLRDGLNLTR 304
Db      181 DEPNHLIIAASLLDLRRINDFEQLVERPAFDSYSLVSPDGEVLLGAAPATGLRDGLNLTR 240
Qy      305 QGVAVQLLSQPENGWLAVYRTDYGNFFRHSRWLVAGLLLT PALLLAGWLGMRWYTSSVVN 364

```

Page 3

Db	361		NWKLFDARGQVPGDICIQVGGRYLQTAFAATRYAGTEAVLCVFNDITVHCEAETALSNAK	420
Qy	484		RAADAASQAKTLFLARMSHEIRTPLYGVLGTLELLDLTTLNERQRAYLRTIQSSSATLMQ	543
Db	421		RAADAASQAKTLFLARMSHEIRTPLYGVLGTLELLDLTTLNERQRAYLRTIQSSSATLMQ	480
Qy	544		LISDVLDVSKIEAGQMALTAAFNPLDLVREVLGNFAASAMAKDLQFYACIDTEVPAQLI	603
Db	481		LISDVLDVSKIEAGQMALTAAFNPLDLVREVLGNFAASAMAKDLQVDPLDTLALAEQVA	540
Qy	604		GDVTRIRQVLNNLVNNALKFTDIGRVVLRVKLLSRNDGRALLQWQVADTGIGIAHEQQR	663
Db	541	: : :	HGFE--ESVLFEVAGGSVGHFEEGV-----GVVEQRLQR	573
Qy	664	: : :	LFEAFYQVSGAHAGGTGLGLSICWHL-----AEMMGHLMVSETGLGSSFSVLVLELP	717
Db	574	: : :	LFQ-----LQRRLLVAHLHEDDRQAPRSGVRRRLGSDPGQVHHIGIVLH--	616
Qy	718	: :	EDEQSGLACRPGLLK	732
Db	617	: :	RDSPATLAAAHGMAK	631

RESULT 3

ADE12146

ID ADE12146 standard; protein; 664 AA.

XX

AC ADE12146;

XX

DT 29-JAN-2004 (first entry)

XX

DE Pseudomonas aeruginosa PvrR-related protein #2.

XX

KW PvrR; bacterial infection; PA14.

XX

OS Pseudomonas aeruginosa; UCBPP-PA14.

XX

PN WO2003004689-A2.

XX

PD 16-JAN-2003.

XX

PF 08-JUL-2002; 2002WO-US021431.

XX

PR 06-JUL-2001; 2001US-0303286P.

PR

16-APR-2002; 2002US-0373233P.

XX

PA (GEHO) GEN HOSPITAL CORP.

XX

PI Ausubel FM, Drenkard E;

XX

DR WPI; 2003-210374/20.

DR

N-PSDB; ADE12145.

XX

PT New isolated PvrR polypeptide and polynucleotide that regulates bacterial

PT

biofilm formation, useful for the diagnosis, prevention and treatment of

PT

gram-negative or gram-positive bacterial infection.

XX

PS Disclosure; SEQ ID NO 6; 185pp; English.

XX

CC The invention comprises the amino acid and coding sequences of the

CC

Pseudomonas aeruginosa PvrR protein. The DNA and protein sequences of the

CC

invention are useful for the diagnosis, prevention, and treatment of

CC

bacterial infection. The present amino acid sequence represents a

CC

Pseudomonas aeruginosa PvrR-related protein of the invention.

XX

SQ Sequence 664 AA;

QY	64	MMDVIREHEVFLGRIARKSDKTTQKYDYDVVPLQRHLLAKENGLAVYEGREFSFAMPFLL	123
Db	1	MMDVIREHEVFLGRIARKSDKTTQKYDYDVVPLQRHLLAKENGLAVYEGREFSFAMPFLL	60
QY	124	ATKHALSADSSGDPFSLGVLLANFYGSFWSVSAYPAPQLLIFDL SGSTR LAVPSIPSTAQ	183
Db	61	ATKHALSADSSGDPFSLGVLLANFYGSFWSVSAYPAPQLLIFDL SGSTR LAVPSIPSTAQ	120
QY	184	RDRLSGSPYPMIVERILARLRTRPVGEDAQRVHWIRADRYRDSALEMLGVARVDLPETLWW	243
Db	121	RDRLSGSPYPMIVERILARLRTRPVGEDAQRVHWIRADRYRDSALEMLGVARVDLPETLWW	180
QY	244	HDEPNHLIIAASLLDLRRINDFEQLVERPAFDSYSLVSPDGEVLLGAAPATGLRDGLNLT	303
Db	181	HDEPNHLIIAASLLDLRRINDFEQLVERPAFDSYSLVSPDGEVLLGAAPATGLRDGLNLT	240
QY	304	RQGVAVQLLSQPENGWLAVYRTDYGNFFRHSRWLVAGLLLT PALLLAGWLGMRWYTSSVV	363
Db	241	RQGVAVQLLSQPENGWLAVYRTDYGNFFRHSRWLVAGLLLT PALLLAGWLGMRWYTSSVV	300
QY	364	NPVHRAHRQLVESDTFSRTLITAPVALVVL TQDDQQLVTCNHLAAQWLGGPTEILGLTS	423
Db	301	NPVHRAHRQLVESDTFSRTLITAPVALVVL TQDDQQLVTCNHLAAQWLGGPTEILGLTS	360
QY	424	NWKLFDARGQVPGDICIQVGGRYLQTAFAATRYAGTEAVLCVFNDITVHCEAETALSNAK	483
Db	361	NWKLFDARGQVPGDICIQVGGRYLQTAFAATRYAGTEAVLCVFNDITVHCEAETALSNAK	420
QY	484	RAADAASQAKTLFLARMSHEIRTPLYGVLTGLELLDLTTLNERQRAYLRTIQSSSATLMQ	543
Db	421	RAADAASQAKTLFLARMSHEIRTPLYGVLTGLELLDLTTLNERQRAYLRTIQSSSATLMQ	480
QY	544	LISDVLDVSKIEAGQMALTAAFNPLDLVREVLGNFAASAMAKDLQFYACIDTEVPAQLI	603
Db	481	LISDVLDVSKIEAGQMALTAAFNPLDLVREVLGNFAASAMAKDLQVDPDLT LALEAQVA	540
QY	604	GDVTRIRQVLNNLVNNALKFTDIGRVVLRVKLLSRNDGRALLQWQVADTGIGIAHEQQR	663
Db	541	HGFE--ESVLFEVAGGSVGHFEEGVV-----GVVEQRLQR	573
QY	664	LFEAFYQVSGAHHAGGTGLGLSICWHL-----AEMMGHLMRVSETGLGSSFSVLVLELP	717
Db	574	LFQ-----LQRRLVVAHLHEDDRQAPRSGVRRRLGSDPGQVHHIGIVLH--	616
QY	718	EDEQSGLACRPGLLK	732
Db	617	RDSPATLAAAHGMAK	631

KW Antibacterial; PvrR; variant *Pseudomonas*; microorganism; gram negative;
KW phenotype-mediated antibiotic-resistance; gram-positive;
KW bacterial infection.